

In re Application of Shan et al.,
S.N. 10/788,825
Filed: 02/27/2004
Attorney Docket No. LA0100

The rejection states that it is not clear what temperature range is considered non-cryogenic. In response, Applicants first note that the converse term, cryogenic, is well understood in the art to mean temperatures that are lower than conventional refrigeration temperatures. For example, temperatures below -100°F (-73.3°C) are commonly considered to be cryogenic. See e.g. Spencer, E. W., *Cryogenic Safety*, <http://www.chemistry.ohio-state.edu/ehs/handbook/gases/cryosafe.htm>. The converse term "non-cryogenic" then could be interpreted as temperatures above -100°F. Applicants, having the right to be their own lexicographer, and not being limited by any confusion as to any chance interpretation of the Specification, have made clear the intended interpretations of the terms "non-cryogenic" and "cryogenic." At page 11, lines 6-11, the Specification of the instant application states that as used therein, the term cryogenic process means a process performed at a temperature of about -20°C or below, characteristically at about -60°C or below; and the term non-cryogenic process means a process performed at a temperature of greater than about -20°C.

The definition provided in the Specification should control the interpretation of this claim term. In fact, this point of law was recently affirmed in an *en banc* decision by the Court of Appeals for the Federal Circuit. See Phillips v. AWH Corporation, --- F.3d ----, 2005 WL 1620331, CAFC (Colo.), July 12, 2005. Accordingly, there is left no room for confusion as to the interpretation of the term used in Applicants' claims, and it would be improper for the Examiner to arbitrarily assign a different interpretation for the purposes of prosecution, as was suggested.

The rejection also notes that the term "carbonyl substituted reactant to form a glycoside" as used in claims 1 and 15 is unclear because not all carbonyl-substituted reactants will form a glycoside on reaction with a lithiated anionic species. Applicants point out in response that the Specification of this application points out that by virtue of the process of the invention,

It has now been found that glycosides in general, and in particular the compounds represented by the general structural formula [I], may be produced at low cost in relatively high yields and with improved purity.

Specification at page 11, lines 18-20, emphasis added. The operation of the invention is made possible by use of a microreactor such as is described in the application at non-cryogenic temperatures, i.e. temperatures above about -20°C, which was before not recognized as possible or feasible for the preparation of glycosides in a way that produces significant product yields. Any glycosides could be prepared, according to the invention, from any carbonyl-

-Page 2 of 12 -

In re Application of Shen et al.,
S.N. 10/788,825
Filed: 02/27/2004
Attorney Docket No. LA0100

substituted compound that is capable of reaction with a lithiated anion to form glycosides. As such, Applicants assert that a limitation as to the exact nature of glycosides formed is not necessary in claim 1. Newly amended claim 15 reflects an embodiment of a continuous process of the invention wherein the glycoside is a compound according to formula IV, as elucidated in Scheme 1.

The rejection further states that the term "microreactor" will be interpreted by the Examiner as any standard glassware. Here again, such an interpretation would fly in the face of the definition carefully laid out by Applicants in the Specification. At page 4, lines 22-26 of the Specification it is explained that a microreactor is a miniaturized reaction system containing one or more reaction channels having sub-millimeter dimensions, and patent references describing such microreactors are enumerated. At page 4, line 28 to page 5, line 9, it is further stated:

Microreactors vary in structure but generally include a series of stacked plates having openings for fluid transfer. The microreactors will have an input port for introduction of reactants and an output port for discharge of a chemical product. In addition, heat transfer fluid pathways are also incorporated into the design to perform a heat exchange function. Using microreactors allows transfer of heat and mass much more quickly than in standard wet chemistry methods, resulting in improved control of rates of reaction and addition of reactants. Specifically, using microreactors allows more accurate control over the reaction temperature of exothermic or endothermic reactions. Additionally, reactants can be heated or cooled immediately upon entry into the reactor. Although microreactors have been used to provide more accurate control of temperature *per se*, they have not traditionally been used to perform those reactions which must be performed under cryogenic conditions. Furthermore, to date, methods of making glycosides using microreactor technology have not been developed.

It is therefore abundantly clear that a microreactor as used in the invention cannot simply be standard laboratory glassware, and it is requested that this assertion be withdrawn.

Based on the foregoing discussion, Applicants submit that the issues raised in the rejection under 35 U.S.C. §112 have been overcome or rendered moot, and the rejection may be withdrawn.

In re Application of Shen et al.,
S.N. 10/788,825
Filed: 02/27/2004
Attorney Docket No. LA0100

The Rejection under 35 U.S.C. §102(b)

The Office action also rejected claims 1, 5, 7, 8, 15, 20, 21 and 22 as being anticipated under 35 U.S.C. §102(b) as being anticipated by Czernecki et al., J. Org. Chem. 1991, 56, 6289-6292 (hereinafter "Czernecki"). Applicants respectfully traverse.

The Office action states that Czernecki teaches the reaction of a carbonyl-substituted compound (1) with the lithiated aromatic compound (3a or 3b) to form the glycoside 5 and 8; and that the lithiated aromatic anion species is prepared by reacting the aromatic compound 2a or 2b (aromatic halide) wherein bromine (a halide) is the leaving group; and that based on such an interpretation of the reference, claims 1, 5, 8, 15, 21 and 22 are anticipated. Applicants respectfully traverse.

Czernecki teaches a batch process for preparation of glycosides at cryogenic temperatures. A complete reading of the reference shows that the reported yield of 98% was obtained only for one of the two steps required for glycosidation, and that it was actually the debenzylolation of the isolated intermediate that produced a 98% yield. The overall yield upon execution of the two steps in the process, lithiation and coupling (followed by debenzylation) is about 60%.

In contrast, the process of the invention, wherein at least the first step of forming the lithiated anion is carried out particularly in a continuous process in a microreactor, produces significantly higher yields after formation of the lithiated anion, coupling and debenzylation are complete. Performing the first and optionally the second steps of the continuous process in a microreactor at non-cryogenic temperatures improves selectivity in the formation of the lithiated anion and glycoside species. See Specification, page 11, lines 6-11. Accordingly, yields of up to about 84% (therefore having a correspondingly lower amount of impurities) have been obtained. See Table 1 below, which shows that comparative evaluation of the batch process described in Czernecki produced yields of about 32% to about 40% at non-cryogenic temperatures, and only showed elevated yield (83.6%) when both lithiation and coupling are performed at cryogenic temperatures (-78°C).

In re Application of Shen et al.,
S.N. 10/788,825
Filed: 02/27/2004
Attorney Docket No. LA0100

Table 1: Preparation of Glycoside

Process	Ex.	Scale (g)	Conditions		Isolated Yield
			Lithiation (solvent, temperature)	Coupling (solvent, temperature)	
Batch processes as run in the standard lab glassware	1	3.0	THF/heptane, -10 °C	THF/heptane -10 °C	40.3%
	2	3.0	THF/heptane, 20 °C	THF/heptane 20 °C	32.2%
	3	3.0	THF/heptane, -78 °C	THF/heptane -78 °C	83.6%
Continuous processes run using a microreactor system (two non-cryogenic steps)	4	4.0	THF/heptane, 20 °C	THF/heptane -10 °C	76.3%
	5	4.0	THF/heptane, 20 °C	THF/heptane 5 °C	72.1%
	6	4.0	THF/heptane, 20 °C	THF/heptane 20 °C	70.4%
Continuous processes run using a microreactor system (non-cryogenic lithiation with cryogenic coupling)	7	4.0	THF/toluene, -10 °C	THF/toluene -78 °C	84.1%

Applicants are prepared to present the above information (submitted here in the interest of timely filing) in declaration format if such is deemed necessary, however it is believed that a comprehension of the sum of all the remarks presented herein should make such *pro forma* action unnecessary.

Based on the foregoing discussion, Applicants submit that each and every element of claims 1, 5, 7, 8, 15, 20, 21 and 22 is not taught or disclosed by Czernecki, therefore there can be no anticipation of any of these claims. Accordingly, this rejection under §102 should be withdrawn and such action is respectfully requested.

In re Application of Shen et al.,
S.N. 10/788,825
Filed: 02/27/2004
Attorney Docket No. LA0100

The Rejection under 35 U.S.C. §103

Claims 1-4, 6, 9-13, 15-19 and 23-27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Czernecki in combination with Hawley's Chemical Dictionary, and Grant & Hackh's Chemical Dictionary. The action states that it would have been obvious to one of ordinary skill in the art to use a non-cryogenic process comprising forming a lithiated anionic species and coupling it with a carbonyl substituted compound to form a glycoside as is instantly claimed, since the reagents, process steps and conditions are taught in the prior art. Applicants respectfully traverse.

Applicants first note that the invention is not rooted necessarily or wholly in the selection of reagents and the general chemistry that generates the glycoside product. Rather, the invention comprises a process wherein the chemical reactions are conducted in whole or in part at non-cryogenic temperatures by virtue of using a microreactor, and neither of these process steps was contemplated for the preparation of glycosides with this chemistry. The action states that Czernecki teaches the lithiation step as well as the coupling step at low temperatures, namely -78°C and -40°C. It is also stated that it is well known in the art to vary process conditions like temperature. However, as pointed out above, these are different from the non-cryogenic conditions specified for the lithiation step, and in certain embodiments also for the coupling step, of this invention. Moreover, Czernecki teaches a batch process which does not demonstrate, suggest or even contemplate the unexpected benefit to be gained from conducting the reactions in a microreactor, one of which is the ability to run the process at higher temperatures than the conventional cryogenic temperatures while producing elevated yield and therefore a purer product. The advantages shown by the results of the claimed process are demonstrated, as discussed above, in Table 1.

The action also states that Czernecki teaches the reaction of carbonyl substituted compound (1) with the lithiated aromatic compound (3a or 3b) to form the glycoside 5 and 8; and that the lithiated aromatic anionic species is prepared by reacting the aromatic compound 2a or 2b (aromatic halide) wherein bromine (a halide) is the leaving group. In response, Applicants point out that the claimed invention comprises performing the chemical reactions responsible for formation of glycoside in a continuous process in at least one microreactor or a series of microreactors.

The action goes on to note that the formation of compound 4 (Table 1) predominates, and that the results should be interpreted to indicate that a very high percentage of the lithiated

-Page 6 of 12 -

In re Application of Shen et al.,
S.N. 10/788,825
Filed: 02/27/2004
Attorney Docket No. LA0100

anionic species is formed which, the Examiner presumes, would automatically translate to a higher amount of the desired glycoside being formed. The Examiner adds that the required species 3 is formed in greater amount at higher temperatures since the corresponding hydrolysis product 4 is obtained in higher yield. The action also focuses on the use of sec-butyl lithium, arguing that one of ordinary skill in the art knows that n-butyl lithium and t-butyl lithium are both used in lithiation reactions, and relies on the definition of "metalating agent" in Hawley's Dictionary. Applicants disagree. As discussed above, the overall yield to be expected from the Czernecki process could be expected to be relatively low, even though there is alleged an example of an 98% yield from a cryogenic lithiation, the overall yield was seen to be on the order of about 60% after execution of the lithiation and coupling steps. In comparison, the process of the claimed invention produces yields of up to 84% at the end of the complete process. The continuous process of the invention using a microreactor could also use n-BuLi or t-BuLi to achieve the lithiation step at non-cryogenic temperatures.

The action also states that Czernecki teaches the use of both THF and toluene in the process; and elsewhere states that Czernecki discloses the use of toluene, petroleum ether and THF. Also in respect of the solvents, the action states that the use of mixtures of aprotic solvents and heptane are obvious variants, and (relying on Grant & Hackh's Chemical Dictionary) that heptane is similar to petroleum ether, which is a mixture of pentanes and hexanes. In response, Applicants note that it may indeed be possible to practice the claimed invention with different solvents, thus the cited references are not dispositive on this point either. Rather, it is the combination of the use of a microreactor at non-cryogenic temperature that produces the unexpectedly improved preparation of glycoside product.

Applicants respectfully request that this rejection for obviousness be withdrawn, it having been properly traversed.

Acknowledgement of Joint Inventorship

Applicants and Assignee acknowledge that the subject matter of the claimed invention and all claims were commonly owned and immediately assigned to the Assignee of record at the time of invention and subsequent thereto.

In re Application of Shen et al.,
S.N. 10/788,825
Filed: 02/27/2004
Attorney Docket No. LA0100

Conclusion

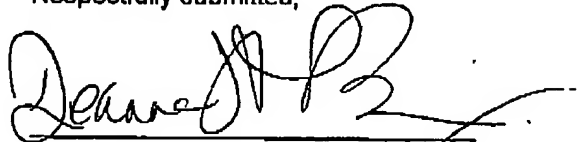
In light of the foregoing amendments and remarks, Applicants submit that all outstanding rejections and observations have been met and overcome, and therefore withdrawal and allowance of the pending claims is requested.

If a direct personal communication might advance the prosecution of this application, the Examiner is invited to contact Applicants' undersigned representative at the telephone number below.

FEE AUTHORIZATION

The Commissioner is authorized to charge any fee required for entry of this amendment, or credit any overpayment thereof to the assignee's Deposit Account No. 19-3880.

Respectfully submitted,



Deanna L. Baxam
Attorney for Applicants
Reg. No. 45,266

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4014
Date: July 18, 2005